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(54) Title: CONTROLLED LOCAL DELIVERY OF CHEMOTHERAPEUTIC AGENTS FOR TREATING SOLID TUMORS

(57) Abstract

A method and devices for localized delivery of a chemotherapeutic agent to solid tumors, wherein the agent does not cross the blood-brain barrier and is characterized by poor bioavailability and/or short half-lives *in vivo*, are described. The devices consist of reservoirs which release drug over an extended time period while at the same time preserving the bioactivity and bioavailability of the agent. In the most preferred embodiment, the device consists of biodegradable polymeric matrixes, although reservoirs can also be formulated from non-biodegradable polymers or reservoirs connected to implanted infusion pumps. The devices are implanted within or immediately adjacent the tumors to be treated or the site where they have been surgically removed. The examples demonstrate the efficacy of paclitaxel, camptothecin, and carboplatin delivered in polymeric implants prepared by compression molding of biodegradable and non-biodegradable polymers, respectively. The results are highly statistically significant.

We claim:

1. A chemotherapeutic composition comprising

a biocompatible polymeric matrix incorporating

an effective amount to inhibit tumor growth when released *in vivo* at the site of the tumor of a water insoluble, relatively lipid insoluble chemotherapeutic agent, wherein the chemotherapeutic agent does not cross the blood-brain barrier in an amount effective to inhibit growth of a solid tumor when administered systemically.

2. The composition of claim 1 wherein the chemotherapeutic agent is paclitaxel or a functionally effective derivative.

3. The composition of claim 1 wherein the chemotherapeutic agent is camptothecin or a functionally effective derivative.

4. The composition of claim 1 wherein the polymer matrix is biodegradable.

7. The composition of claim 4 wherein the polymeric matrix is formed of a polymer selected from the group consisting of polyanhydrides, polyhydroxy acids, polyphosphazenes, polyorthoesters, polyesters, polyamides, polysaccharides, polyproteins and copolymers and blends thereof.

8. The composition of claim 1 wherein the polymeric matrix is formed of ethylene vinyl acetate.

9. The composition of claim 1 further comprising biologically active compounds selected from the group consisting of other chemotherapeutics, antibiotics, antivirals, antiinflammatories, targeting compounds, cytokines, immunotoxins, anti-tumor antibodies, anti-

angiogenic agents, anti-edema agents, radiosensitizers, and combinations thereof.

10. A method of administering to a patient in need of treatment a water insoluble, relatively lipid insoluble chemotherapeutic agent comprising

administering an amount of the chemotherapeutic agent effective to inhibit growth of a solid tumor locally near or in the tumor,

wherein the systemic administration of the same dosage of chemotherapeutic agent is not effective to treat tumors and wherein the chemotherapeutic agent does not cross the blood-brain barrier in an amount effective to inhibit growth of a solid tumor when administered systemically.

11. The method of claim 10 wherein the chemotherapeutic agent is paclitaxel or a functionally effective derivative.

12. The method of claim 10 wherein the chemotherapeutic agent is camptothecin or a functionally effective derivative.

13. The method of claim 10 wherein the chemotherapeutic agent is locally delivered by direct infusion to the tumor from a reservoir.

14. The method of claim 10 wherein the chemotherapeutic agent is locally delivered by implantation of a biocompatible polymer matrix incorporating the chemotherapeutic agent.

15. The method of claim 14 wherein the polymer matrix is biodegradable.

16. The method of claim 15 wherein the polymeric matrix is formed of a polymer selected from the group consisting of polyanhydrides, polyhydroxy acids, polyphosphazenes, polyorthoesters, polyesters, polyamides, polysaccharides, polyproteins, and copolymers and blends thereof.

17. The method of claim 14 wherein the polymeric matrix is formed of ethylene vinyl acetate.

18. The method of claim 10 further comprising administering radiation in combination with the composition.

19. The method of claim 10 further comprising administering with the chemotherapeutic agent biologically active compounds selected from the group consisting of other chemotherapeutics, antibiotics, antivirals, antiinflammatories, targeting compounds, cytokines, immunotoxins, anti-tumor antibodies, anti-angiogenic agents, anti-edema agents, radiosensitizers, and combinations thereof.

20. The method of claim 10 wherein the composition is in the form of micro-implants and are administered by injection or infusion.

21. A method for treating brain tumors comprising administering to the tumor an effective amount of a platinum based chemotherapeutic at a dosage of between 0.1 and 5% loading by weight or less.

22. A composition for treating brain tumors comprising a platinum based chemotherapeutic at a dosage of between 0.1 and 5% loading by weight.